IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Haim AVIV et al.	Confirmation No. 6729
Application No.: 10/644,687	Group Art Unit: 1626
Filing Date: August 19, 2003	Examiner: Taofiq A. Solola
For: HIGH ENANTIOMERIC PURITY DEXANABINOL FOR PHARMACEUTICAL COMPOSITIONS	Attorney Docket No.: 87754-7500

DECLARATION OF RAPHAEL BAR

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

1. I am a citizen of Israel and currently reside at 49 Menuha Venahala Street, Rehovot 76247, Israel.

2. I hold a Ph.D. Degree in Applied Chemistry, received from The Hebrew University of Jerusalem, Israel, in 1984.

3. I am an employee of Pharmos Limited ("Pharmos"), an Israeli company having a place of business at Kiryat Weizmann, Rehovot 76326, Israel.

4. My present title at Pharmos is Senior Director of Analytical Development and I have held this position for about a year. I have worked in the Analytical Department of Pharmos for about seven years. I have ten years of experience in the development and use of analytical methods for research and development of new drug candidates, especially regarding cannabinoids.

5. I am a co-inventor of the above-identified patent application, I have reviewed the Final Office Action and have been asked to provide my expert opinion regarding two objections of the Examiner. The first one relates to the question whether the "Mechoulam sample" used in the side-by-side comparison with "Ultrapure sample" represents a true Kloog sample as disclosed in U.S. Patent No. 5,284,867. The second point relates to the assertion of the

Examiner that the values of the enantiomeric excess of "Mechoulam sample" and "Ultrapure sample", 99.4% and 99.9% respectively, are within experimental error.

6. The laboratory scale synthesis of HU-211 (dexanabinol) is disclosed in U.S. Patent No. 4,876,276 to Mechoulam et al. ("Mechoulam") wherein the dexanabinol compound is claimed. U.S. Patent No. 5,284,867 to Kloog et al. ("Kloog") does not teach the synthesis of HU-211, but discloses in its Preparatory Example that the acetylation of HU-211 results in a mixture of non-acetylated (HU-211), mono-acetylated (HU-247 and compound B) and bi-acetylated (compound B) derivatives of dexanabinol, and teaches that the acetylated compounds A and B can be reduced to recover the starting material HU-211.

It is my understanding that the starting dexanabinol material used in U.S. Patent No. 5,284,867 was prepared by Professor Raphael Mechoulam who is a co-inventor of said patent. Therefore, a "true" Kloog sample is a sample prepared according to the original synthetic procedure of Mechoulam.

The "Mechoulam sample" that was used in the side-by-side comparison is a laboratory scale batch of HU-211 prepared according to Mechoulam's original synthetic procedure with minor modifications. Thus, in my opinion "Mechoulam sample" is either equivalent or superior to a "true" Kloog sample and therefore a "true" side-by-side comparison, were original samples available, would have been even more favorable to the Ultrapure sample.

7. The values of 99.4% and 99.9% that the Examiner considers as being within experimental error of one another do not represent absolute amounts of HU-211, but enantiomeric excess (e.e.) of HU-211 in a drug substance that may contain the opposite enantiomer HU-210. Thus, the enantiomeric excess is not strictly speaking an experimental value, but a calculated one derived from the following formula:

$$\text{percent e.e.} = 100*([\text{HU-211}]-[\text{HU-210}])/([\text{HU-211}]+[\text{HU-210}])$$

wherein the concentration of the enantiomers is separately determined by HPLC and expressed as percent weight by weight. The absolute amounts of HU-211 and HU-210 in "Mechoulam sample" and a representative "Ultrapure sample" are tabulated below.

Sample	HU-211	HU-210	EE
Mechoulam	91.1%	0.26%	99.4%
Ultrapure	98.8%	0.02%	99.9%

The Examiner's assertion regarding the reliability of the above-discussed values is in my opinion incorrect for three reasons, discussed separately below.

8. First and foremost, it is my understanding that the biological results achieved in the side-by-side comparison prove without a doubt that the small mathematical difference between the enantiomeric excess of the two samples have remarkable consequences. Animals administered i.v. with 50 mg/kg of "Mechoulam sample" (e.e. 99.4%) displayed dramatic hypothermia (drop of about 6°C in rectal temperature), catalepsy (30 sec. immobility on a beam) and locomotor inhibition (~94%), in contrast with the animals injected with the "Ultrapure sample" (e.e. 99.9%) in which side effects were totally absent. Thus, from the aspect of the biological activity, 99.4% and 99.9% are clearly not "within experimental error".

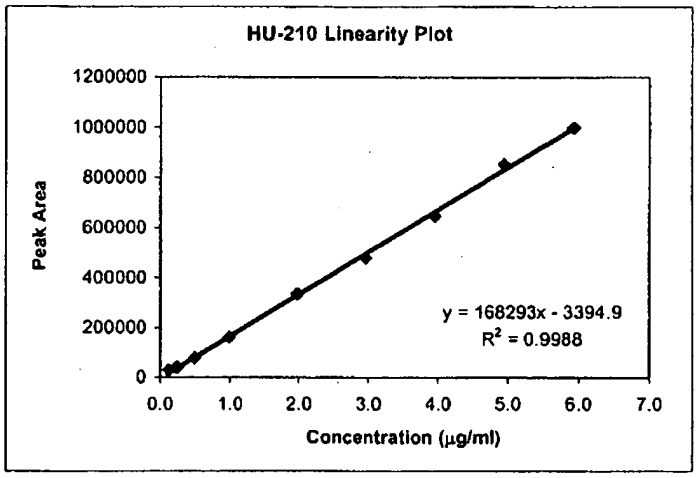
These serious adverse events are caused by the presence of only 0.26% w/w of HU-210 in "Mechoulam sample", which emphasizes the need for a different route of synthesis to achieve the purity (both absolute and enantiomeric) appropriate for clinical use of dexanabinol. The original synthetic route of Mechoulam did not allow for the preparation of a compound that fulfill the present drug substance specification of above 98% absolute amount of HU-211 and below 0.05% absolute amount of HU-210, together with an enantiomeric excess of above 99.9% for HU-211.

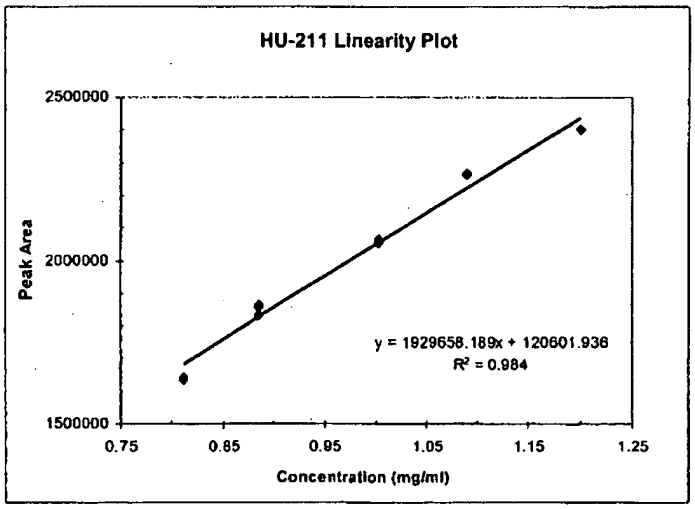
9. From a mathematical aspect, the above table clearly demonstrates that though 99.4 and 99.9% might seem highly similar, these values referring to the calculated e.e. do not reflect that the original absolute amounts of the individual enantiomers are themselves far from being "within experimental error" of one another. The content of HU-211 differs in the two samples by more than 7.5% in absolute values, and the content of HU-210 by more than 10-fold, which is above any "experimental" variation a person skilled in the art would accept when using robust validated analytical methods.

10. From an analytical aspect, the HPLC methods disclosed in the present application, which were purposefully developed to achieve this goal, are accurate and sensitive enough to distinguish between the absolute amounts of HU-210 and HU-211 in the samples tested. In my opinion, the methods previously disclosed were not sensitive enough to accurately determine the amount of these enantiomers, especially the concentration of the minor constituent

HU-210. As detailed in the above-referenced application, the analytical methods of the invention lead to a significant improvement of detectability of HU-210 as expressed by an approximated decrease of over 30-fold in the lower limit for reliable quantitation of HU-210, which can now be detected at a concentration of 0.125 μg/ml.

To illustrate the accuracy of the present analytical methods, I enclose two plots depicting the linearity of HU-210 and HU-211 measurements obtained in representative analysis. In both cases at least five solutions comprising known amounts of HU-210 or HU-211 were prepared and injected. The amount of HU-210 and HU-211 was determined as described in the specification in Example 3 and the peak area of each sample was plotted against sample concentration. The data were subjected to linear regression analysis resulting in linear equations and R-square values which are indicated on each plot.





Such graphs demonstrate that the methods disclosed in the present application to assess the absolute amounts of HU-210 and HU-211, and consequently the enantiomeric purity of clinical grade dexanabinol, are accurate and sensitive. Therefore, the absolute amounts of HU-210 and HU-211 in the samples tested in the side-by-side comparison are not "within experimental error" nor is the subsequent e.e.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

Dated: 02-Mar-06

Raphael Bar
Senior Director of Analytical Development